

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

<p>In re Application of <i>Lee et al.</i> Serial No.: 10/666,689 Filed: September 19, 2003 Title: HUMAN PF4A RECEPTORS (as amended)</p>	<p>Group Art Unit: 1646 Examiner: John Ulm Confirmation No: 2217 Customer No: 09157 Electronically Filed on October 5, 2007</p>
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SECOND DECLARATION OF JAMES LEE, P.H.D. UNDER 37 C.F.R. § 1.132

Sir:

I, James Lee, Ph.D. declare and say as follows:

1. I am a Principal Research Associate at Genentech, Inc., South San Francisco, CA 94080.
2. I am one of the inventors of the above captioned patent application.
3. I appreciate that the claims in the above captioned patent application have been rejected for lacking a specific, substantial and credible utility under 35 U.S.C. § 101. On April 14, 2006, I previously attested as to how the PF4AR polypeptides of this invention (SEQ ID NO:6 and variants thereof), would be appreciated by one of skill in the art to play a key role in regulating inflammation. 4/14/2006 Lee Affidavit, para. 8.
4. I further understand that the Examiner has maintained the rejection under 35 U.S.C. § 101, and even after my prior attestation, remains unconvinced after my prior attestation, in part because there is no evidence in the specification showing that the exogenous administration of or agonist activation of a

receptor of the present invention actually induces an inflammatory response. Office Action of 4/6/2007, page 3. While I still strongly disagree with the Examiner's conclusion as well as the assertions that the previously asserted utility of inflammatory is not specific and substantial, I wish to clarify and characterize the utility of the polypeptides of the invention as a marker for inflammation.

5. I, along with the other inventors of the above captioned patent application, conceived of the PF4AR polypeptides, including the molecule of Figure 5 (SEQ ID NO:6) and variants thereof, as a new member of the platelet factor 4 superfamily. This molecule is now known as CXCR-5. Moreover, we further recognized and disclosed that this molecule would also be a mediator of inflammation. We came to this conclusion based, at least in part, on (a) the shared structural features of the above PF4AR polypeptide to the IL-8R ("CXC" family), specifically (i) the proximity of the N-terminal cysteine residues (*i.e.*, "CXC" v. "CC"); (ii) the shared TM structural components (discussed in the specification at page 15, lines 13-25) and (iii) the use of the IL-8R to isolate the PF4AR polypeptide, and (b) our understanding of the prior art.
6. At the time of the filing of the present invention, the prior art recognized that PF4AR polypeptides, now known as "CXC and CC" chemokines, were mediators of inflammation. For example, the review articles Stoeckle *et al.*, *New Biologist*, 1990, 2(4): 313-323 and Miller *et al.*, *Crit. Rev. Immunol.*, 1992, 12(1,2):17-46 both verify that the state of the art at the time of filing recognized that CXC chemokines played important roles in regulating inflammation. It follows that any such polypeptide that is recognized as a regulator of inflammation, would most certainly be recognized as a marker of inflammation. Indeed, this fact was recognized by me along with my co-inventors and was a significant reason why we filed for patent protection of the polypeptides of the invention.

7. It is presently understood that chemokines regulate inflammation because they are the primary regulatory molecules of leukocyte trafficking. This understanding is illustrated in Sabroe *et al.*, *Eur. Respir. J.*, 2002, 19:350-355 and Luster *et al.*, *Nature Immunol.*, 2005, 6(12): 1182-1190. That is, the expression of the polypeptides of the invention in a tissue sample is indicative of the presence of leukocytes, which in turn means activation of inflammation. Of particular note is that both of these relatively recent review articles corroborate Applicants claim that chemokines, and specifically the polypeptides of the invention (e.g., CXCR-5) as being a particular molecular determinant in leukocyte trafficking. (Sabroe at 351; Luster at 1187).
8. The involvement of chemokines in the chronic inflammatory disorder rheumatoid arthritis was reviewed by Shadidi, *Biodrugs* 18(3): 181-187 (2004). CXCR-5 was specifically identified as the key receptor on B-cells for the development of follicles and lymphoid structures in the synovium, which is predictive of a more severe clinical arthritis. Shadidi at page 183. This was further confirmed by Schmutz *et al.*, *Arthritis Res. Ther.* 2005, 7:R217-R229 that CXCR-5 expression is significantly upregulated in synovial tissue isolated from rheumatoid arthritis patients. Thus, this further confirms that CXCR-5 (*i.e.*, SEQ ID NO:6) is a specific marker for the inflammatory disorder rheumatoid arthritis. This disorder is specifically enumerated in the specification on page 14, line 14.
9. It is my considered scientific opinion that the evidence set forth in the present declaration corroborates the stated utility of the PF4AR polypeptide CXCR-5 (SEQ ID NO:6) and variants thereof, as markers of inflammation, and that this evidence is specific, credible and substantial. In light of the disclosure in the specification, one of ordinary skill would have appreciated and understood the association of CXCR-5 with inflammation as of the filing date. As the understanding of chemokine receptors has developed over time, the

connection between inflammation and chemokines in general, as well as CXCR-5 specifically, has been scientifically corroborated and verified, as summarized above.

10. I hereby declare that all statements made herein are of my own knowledge, are true, and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Signed: _____

James Lee

Date: 2007 October 4